follows. A marked up version of amended claim 11 wherein the deleted material is in brackets and the inserted material is underlined is attached hereto as **Exhibit B**:

--11. (2x Amended) The method of claim 1, wherein the peptide derivative of step (a)(i) comprises an alkyl derivative. --

REMARKS

Claims 1-57 are pending in the subject application. Applicants have hereinabove canceled claims 3, 9, 10, 14, 16, 19, 23, and 30-57 without prejudice or disclaimer to applicants right to pursue the subject matter of these claims in a later-filed application. This amendment does not involve any issue of new matter. Therefore, entry of this amendment is respectfully requested such that claims 1, 2, 4-8, 11-13, 15, 17, 18, 20-22 and 24-29 will be pending.

Objection to the specifications

The Examiner objected to the specification because of the following alleged informalities: The Examiner stated that the word peptide on page 13, line 3, has not been corrected.

In response, applicants have amended the specification in accordance with the Examiner's suggestion such that page 13, line 3 recites **peptide** and not **pepetide**. Applicants contend that this amendment obviates the above objection and respectfully request that the Examiner reconsider and withdraw this objection.

Objection to claim 11

The Examiner objected to claim 11 because of the following alleged informality: The Examiner stated that the word "derivitive" should be spelled "derivative" on page 48, line 28. The Examiner stated that appropriate correction is required.

In response, without conceding the correctness of the Examiner's position, but to expedite prosecution of the subject application, applicants have herein amended claim 11 such that it now reads "derivative." Applicants contend that this amendment obviates the above objection and respectfully request that the Examiner reconsider and withdraw this objection.

Rejections under 35 U.S.C. § 112, first paragraph

The Examiner rejected claims 11 and 12 under 35 U.S.C. §112, first paragraph, alleging that the specification, while being enabling for a method for determining whether a compound is capable of inhibiting the interaction of a peptide with a receptor for advanced glycation end product (RAGE) in a competitive assay using a peptide that is a carboxyl-lysine-modified AGE, does not reasonably provide enablement for a peptide derivative comprising an alkyl group. The Examiner stated that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

The Examiner stated that claims 11 and 12 encompass the competitive

binding assay of claim 1, in which the peptide derivative of step (a)(i) comprises an alkyl derivative, which can be an acetyl derivative, a propyl derivative, an isopropyl derivative, a butyl derivative, an isobutyl derivative, or a carboxymethyl derivative. The Examiner states that the specification teaches a number of experiments that were performed to elucidate the specific binding of AGE peptides to a RAGE, or the effects of these AGE peptides on various cell types (Figures 1-7 and pages 4-6 of the specification). The Examiner states however, that the only AGEs that were used in these experiments were carboxy-lysine (CML), pentosidine, and methylgloxal modified proteins. The Examiner states that in figure 1 and in the Brief Description of the Drawings on page 4 and the results section on pages 33-34, it was demonstrated that in the radioligand binding assays in which CML-BSA, pentosidine-BSA or methylglyoxal-human serum albumin were tested, only CML-BSA specifically bound to RAGE. Both pentosidine-BSA and methylglyoxal-HSA did not bind specifically to RAGE. The Examiner stated that similar results were found in the other experiments shown in Figures 2-7 and in the results section. The Examiner stated that there were no experiments performed with a peptide comprising an alkyl derivative. The prior art does not disclose that peptides comprising an alkyl derivative are AGEs, or that they would bind to RAGE.

The Examiner stated that it is not disclosed and not predictable from the limited teachings of the prior art and specification that a peptide comprising an alkyl derivative would bind RAGE and

function in a competitive binding assay, as claimed. The Examiner stated that there is no guidance in the specification that such compounds would bind to RAGE, and the specification has not disclosed a single working example showing that such derivatives would bind. The Examiner stated that it is not predictable, based on the information provided in the specification or from the prior art, that the claimed compositions could be used in such assays, especially in light of the experimental results that teach only the carboxymethyl-lysine-modified peptide specifically bound to RAGE. The Examiner stated that the specification has not provided the person of ordinary skill in the art the guidance necessary to be able to use a peptide comprising an alkyl derivative in the assay as claimed. The Examiner stated therefore, that the method of using such derivatives is not enabled.

In response, applicants respectfully traverse Examiner's rejection of claims 11 and 12 under 35 U.S.C. 112, first paragraph. Applicants' assert that one skilled in the art of chemical derivitization, a technique utilized to alter critical amino groups of AGEs to elucidate specific AGE/RAGE binding, would be able to create peptides, wherein amino groups of the peptide are inactivated, based on the disclosure of the subject application. Applicants point out that "inactivation by derivitization" is described in applicants' specification at page 12, lines 21-31, specifically citing examples of such chemical modifications, including making an alkyl derivative, all of which would be known to one of skill in the art. Applicants contend that these comments

obviate the above rejection and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Rejection under 35 U.S.C. § 112, first paragraph

The Examiner rejected claim 29 under 35 U.S.C. 112, first paragraph, as based on a disclosure which is not enabling. The Examiner stated that the step of admixing a peptide, RAGE or a fragment thereof and a compound to be tested inside a cell, is critical or essential to the practice of the invention, but not included in the claim and is not enabled by the disclosure. The Examiner directed the applicant to see *In re Mayhew*, 527F.2d 1299, 188 USPQ 356 (CCPA 1976).

The Examiner stated that claim 29 requires that a competition assay for determining whether a compound is capable of inhibiting the interaction of a peptide with a receptor for advanced glycation end product (RAGE) in a competitive assay, comprises admixing the peptide with RAGE or a fragment of RAGE in the presence and the absence of the compound in a cell, which is interpreted to mean they are admixed inside the cell. The Examiner stated that the specification on page 9, lines 34-35, states "In another embodiment of the screening method, the admixing of step (a) occurs in a cell.", but there is no other information in the disclosure as to how these components can be introduced into a cell nor how the amount of the peptide bound to the RAGE could be determined. The Examiner stated that it is not commonly practiced in the art that competition binding experiments are performed inside cells; however

competition binding experiments in which one component is present on the outside of the cell are well known in the art. The Examiner stated that the specification has not taught the skilled artisan how to introduce these three components inside a cell in a manner in which they can freely interact and then determine the amount of binding, and the prior art has also not taught how to accomplish this type of assay. The Examiner stated that therefore, claim 29 is not enabled for competition assays performed inside a cell.

In response, applicants respectfully traverse Examiner's above rejection. Applicants maintain that one skilled in the art of competition assays for determining whether a compound is capable of inhibiting the interaction of a peptide with a receptor for advanced glycation end product (RAGE) would understand the specification on page 9, lines 34 and 35, "In another embodiment of the screening method, the admixing of step (a) occurs in a cell," to be sufficiently enabling to carry-out in vitro experiments when viewed in light of page 9, line 20, i.e. "the screening method may be carried out in vitro, wherein one or more of the components are attached or affixed to a solid surface, or wherein the components in step a are admixed inside of a cell." Applicants contend that these comments obviate the above objection and respectfully request that the Examiner reconsider and withdraw this objection.

Rejections under - 35 USC § 102(e)

The Examiner rejected claims 1, 2, 5-8, 13, 15, 17, 18, 20-22 and 24-28 under 35 U.S.C. 102(e) as being anticipated by Morser et al.,

U.S. patent No. 5,864,018, filed April 16, 1996, for reasons cited in the previous Office Action, Paper No 9, at pages 6-8.

The Examiner stated that claims 1, 2, 5-8, 13, 15, 17, 18, 20-22 and 24-28 encompass a method for determining whether a compound is capable of inhibiting the interaction of a peptide with a receptor for advanced glycation end product (RAGE) in a competitive assay, and the reasons for rejection were discussed in the previous Office Action. The Examiner stated that the applicants traverse the rejection, and assert that Morser, et al. does not disclose every limitation of Applicant's claimed invention, and specifically does not describe that the amino groups of the peptide in the competition assay are inactivated by chemical derivatization. The Examiner stated that the applicants point out that "inactivated by derivatization" is described in Applicants' specification at page 12, as encompassing a chemical modification of a peptide so as to cause amino groups of the peptide to be less reactive with chemical modification than without such chemical modification. The Examiner stated that the Applicants assert that Morser et al. Does not disclose peptides so modified and therefore does not disclose Applicants' claimed method.

The Examiner stated that the Applicant's arguments have been considered but are found not persuasive. The Examiner stated that Morser et al., in column 21, Example 2, describes the preparation of AGE-BSA, by incubating bovine serum albumin with ribose in the presence of PMSF. The Examiner stated that this is a chemical

derivatization, and though Morser et al. does not specifically state that the amino groups of the BSA are less reactive with the chemical modifications than without such chemical modifications, this is inherent property of such a derivatized protein. The Examiner stated that therefore, this modified peptide meets the limitations of the claims, and the rejection of claims under 35 USC §102(e) is maintained.

In response, applicants respectfully traverse Examiner's above rejection. Applicants' maintain that Morser et al. does not disclose every limitation of applicants' claimed invention for reasons cited in the previous response to July 10, 2001 Office Action, at pages 11 and 12. Applicants contend that these comments obviate the above objection and respectfully request that the Examiner reconsider and withdraw this objection.

Rejection under - 35 USC § 103(a)

The Examiner rejected claim 4 under 35 U.S.C. 103(a) as being unpatentable over Morser et al. and further in view of Reddy et al., Biochemistry, Vol.34,pp 10872-10878, 1995, for reasons cited in the previous Office Action, Paper No 9, at pages 9-10.

The Examiner stated that the rejection over claims 11 and 12 has been withdrawn because the prior art does not disclose a method for determining whether a compound is capable of inhibiting the interaction of a peptide with a receptor for advanced glycation end product (RAGE) in a competitive assay using a peptide comprising an

alkyl derivative. The Examiner stated that however, claim 4 remains rejected for the carboxymethyl-lysine-modified peptides in the assay method.

The Examiner stated that the applicants argue on pages 16-17 that inhibiting one particular interaction between a particular peptide and RAGE does not enable one to accurately determine which potential compounds are capable of inhibiting the interaction of one or more of the many other potential peptide-RAGE combinations, and that one would therefore not be motivated based on the cited references to choose a particular peptide/RAGE interaction for which to determine which compounds might be capable of inhibiting that interaction. The Examiner stated that the applicants further stated that using the AGE described in Reddy in the method described in Morser does not include the limitations or steps recited in the claims of applicants' presently claimed invention, and therefore, applicants maintain that the Morser and Reddy references, either alone or in combination, do not render obvious applicant's claimed invention.

The Examiner stated that the applicants's arguments have been considered but are not found persuasive. The Examiner stated that since Morser et al. teaches all of the steps and limitations of the assay with the exception of using carboxymethly-lysine-modified peptides in the assay method, and Reddy et al. teaches that carboxymethly-lysine is a dominant advanced glycation end product (AGE) antigen in proteins, and given that carboxymethyl-lysine-

modified peptides are a dominant AGE, it would have been *prima facie* obvious to one of skill in the art of AGE/RAGE art at the time of the invention to use a carboxymethly-lysine-modified peptide of Ready as the AGE in the AGE/Rage competition assay of Morser et al. to determine whether a compound is capable of inhibiting the AGE/RAGE interaction. The Examiner stated that therefore, the rejection of claim 4 under 35 U.S.C. 103(a) is maintained.

In response, applicants respectfully traverse Examiner's rejection of claim 4 under 35 U.S.C. 103(a). The mere fact that references can be combined does not make the resultant combination obvious unless the prior art also suggests the desirability of the combination. The applicants contend that the prior art does not suggest the desirability of the combination of Reddy et al. and Morser et al. when viewed well within the ordinary skill of the art at the time the claim was made. Therefore, applicants contend that the Examiner used impermissible hindsight when combining Morser et al. and Reddy et al. to demonstrate *prima facie* obviousness in claim 4. While Reddy et al. teaches that carboxymethyl-lysine is a dominant advanced glycation end product (AGE) antigen in proteins, and that given that carboxymethyl-lysine-modified peptides are a dominant AGE, it would not have been *prima facie* obvious to one skilled in the art of AGE/RAGE art at the time of the invention to use a carboxymethyl-lysine-modified peptide of Reddy et al. as the AGE in the AGE/RAGE competition assay of Morser et al. Further, applicants point out that Reddy et al. demonstrates

antigentic dominance of the N^{e} - (Carboxymethyl)lysine form of AGE in tissue prcteins, not the specificity of its binding to RAGE. And, Lander et al., and Yan et al. demonstrate a complex experimental landscape of heterogeneous AGE/RAGE interactions mediated by oxidant stress. Accordingly, combining knowledge of antigenic dominance of a particular peptide with knowledge of the state of the work within in a field of complex heterogeneous AGEs, does not necessarily enable one of ordinary skill in the art to determine AGE/RAGE binding efficiency. Applicants contend that these comments obviate the above rejection and respectfully request that the Examiner reconsider and withdraw this objection.

Summary

For the reasons set forth hereinabove, applicants respectfully request that the Examiner reconsider and withdraw the various grounds of objection and rejection and earnestly solicit allowance of the now pending claims, i.e. claims 1, 2, 4-8, 11-13, 15, 17, 18, 20-22 and 24-29.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone either of them at the number provided below.

No fee, other than the enclosed $445.00 fee for a three-month extension of time, is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is

required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.

9/27/01

John P. White
Reg. No. 28,678

Date

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Exhibit A

In the specification

Page 12, line 33 to page 13, line 10

--In one embodiment of the present invention is a screening assay for identifying a compound capable of inhibiting interaction of a peptide with the AGE binding site of RAGE (e.g., the V-domain or the minimal necessary amino acid sequence required to have binding of an AGE) which comprises: (a) admixing the peptide and a second [pepetide] peptide which has the sequence of the AGE binding site of RAGE and the compound; (b) determining the amount of the peptide bound to the second peptide, and (c) comparing the amount of bound peptide determined in step (b) with the amount determined in the absence of the compound, thus identifying the compound as capable of inhibiting the interaction of the peptide with the AGE binding site of RAGE. --

Exhibit B

In the claims

--11. (2x Amended) The method of claim 1, wherein the peptide derivative of step (a)(i) comprises an alkyl [derivitive] derivative. --